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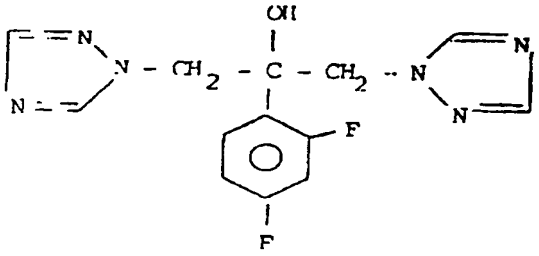
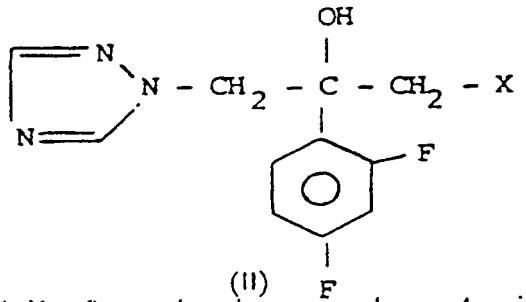
(54) Título: **Procedimiento para la preparación de triazolil-isopropanol.**

(57) Resumen:
Procedimiento para la preparación de triazolil-isopropanol de fórmula I



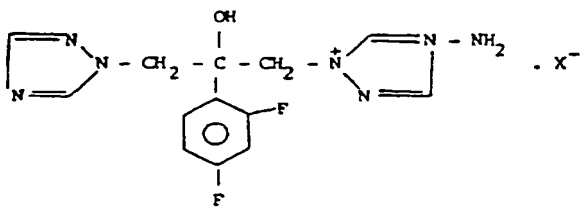
(I)

que comprende la reacción de un compuesto de fórmula



(II)

donde X es fluoro, cloro, bromo o yodo, con 4-amino-1,2,3-triazol, para dar el compuesto de fórmula III

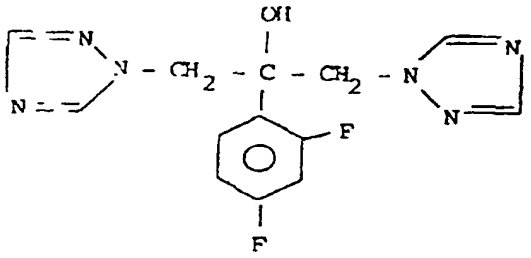


(III)

que se hace reaccionar con ácido nitroso.

DESCRIPCION

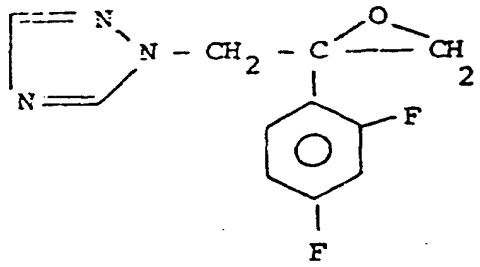
La presente invención tiene por objeto un procedimiento para la preparación del 2-(2,4-difluorfenil)-1, 3 bis-(1H,1,2,4-triazol-1-il)-2-propanol, de fórmula (I)



(I)

El compuesto (I), conocido también con el nombre común de fluconazol, es un fármaco de actividad antimicótica, descrito en la patente británica nº 2.099.818.

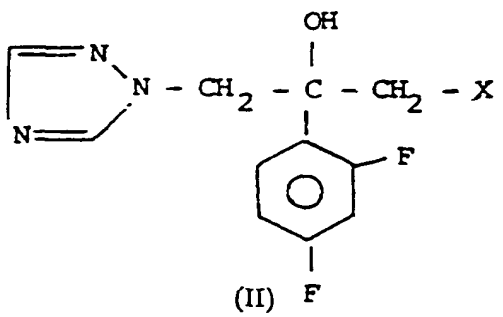
Los procedimientos para la preparación del compuesto (I) conocidos hasta ahora se caracterizan por la apertura de un intermedio epoxídico de fórmula



con 1,2,4-triazol.

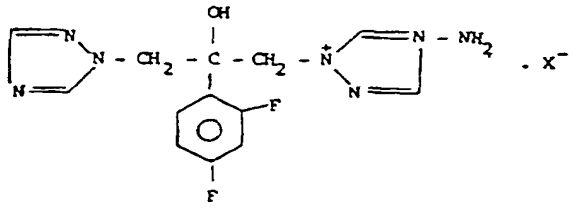
Esta reacción, sin embargo, no es selectiva, y dá lugar a la formación del isómero 2-(2,4 - difluorofenil), 1 - (1H,1,2,4 - triazol- 1 -il),3 - (4H,1,2,4 - triazol - 4 - il),2 - propanol.

Se ha hallado ahora que se puede obtener el compuesto, selectivamente, por reacción de una halogenohidrina de fórmula II



(II)

donde X es fluoro, cloro, bromo o yodo con 4-amino-1,2, 4-triazol, para dar el compuesto III



(III)

donde X es según se define arriba, que, por reacción con ácido nitroso en ambiente acuoso o acuoso-alcohólico, conduce al compuesto I a elevados grados de rendimiento y pureza. El compuesto III es nuevo y constituye objeto de la invención a título de intermedio.

El compuesto II es fácilmente obtenible a partir de 1-bromo-2,4-difluoro-benceno por reacción con 1, 3-dicloroacetona y, por ende, con 1H-1,2,4-triazol o bien a partir de α-difluoro-acetona por reacción con 1-clorometil-1H-1,2,4-triazol (Synthesis 1983, 647), o bien igulmente a partir de 1-(2-(2,4-difluoro-fenil) -2,3-epoxipropil)-1H-1,2,4-triazol por reacción con ácidos halogenohídricos.

La reacción entre el compuesto II y el 4-amino -1,2,4-triazol se lleva a efecto de preferencia en disolventes inertes como alcoholes C_1-C_5, cetonas, ésteres, éteres.

Los siguientes ejemplos ilustrarán mejor la invención:

Ejemplo 1.

2(2,4-difluorofenil),1-bromo,3-(1H,1,2,4-triazol-1-il) 2 -propanol, (II con X = Br).

Se toman 19,4 g de 2(2,4-difluorofenil),1-(1H, 1,2,4-triazol-1-il)-2,3-epoxi-2-propanol metansulfonato y se tratan con 81 g de ácido bromhídrico concentrado a temperatura ambiente, durante 1 hora, y se añaden 180 cm^3 de agua y carbonato sódico hasta la precipitación del producto.

Se extrae con un total de 300 cm^3 de metilenocloruro y se concentra en seco, recogiéndose el resíduo con 35 cm^3 de mezcla de agua y metanol 1/1; se agita después hasta la completa cristalización del producto en cuestión.

Se obtienen 12,5 g de producto seco, de las siguientes características:

Fórmula bruta:	$C_{11}H_{10}BrF_2N_3O$
Peso molecular:	318,119
Punto de fusión:	120°C
Análisis elemental:	C teor. 41,53% hallado 41,84%
	H teor. 3,17% hallado 3,19%
	N teor. 13,21% hallado 13,15%
Masa: fragmento	320 Molecular + 2
	318 Molecular
	238 -HBr
	235 - Triazolilmetileno
	224 -HBr e - metileno

RMN: en $CDCl_3$

ppm 8	individual	1 H	Triazol
" 7,8	"	1 H	Triazol
" 7,5	sist.complejo	1 H	Aromático
" 6,8	"	2 H	
" 4,7	doble-doble	3 H	Metileno s/Br. e hidroxilo
3,8	cuarteto	2 H	" s/Triazol

I.R.: atribuciones principales

cm-1 3150	estirado	-OH
" 3120	"	-H aromáticos
" 1600+1620	"	C=C arom. y CN
" 1135	"	C-O- alcohol terc.
" 860	deformación	-H arom. por 2 H adyacentes.

Ejemplo 2.

2-(2,4-difluorofenil) ,1-(1H,1,2,4-triazol-1-il), 3-(4H,4 -amino,1,2,4-triazonio-1-il)2-propanol, bromuro (III).

Se toman 6,4 g de 2(2,4-difluorofenil),1-bromo, 3-(1H,1,2,4-triazol-1-il)-2-propanol y se hacen reaccionar hasta reflujo en 100 ml de alcohol isopropílico con 5,1 g de 4-amino-1,2,4-triazol durante 8 horas. Se enfría la mezcla de reacción a O°C y se filtra el producto que cristaliza. El producto bruto húmedo así obtenido se trata hasta reflujo con 50 ml de alcohol isopropílico, se enfría, se filtra y se seca al vacío, a 40°C.

Se obtienen 6,3 g (77,8% de la teoria) del producto citado, que presenta las siguientes características:

Fórmula bruta: $C_{13}H_{14}BrF_2N_7O$

Peso Molecular: 402,2

Análisis elemental: C teór. 38,82% hallado 38,40%
H teor. 3,51% hallado 3,66%
N teor. 24,38% hallado 24,14%

Masa:fragmento 224-Br-Aminotriazol-Metileno
141 Procedente-Triazolilmetileno
127 Catión difluorbencílico
113 Difluobenceno
82 Catión triazolilmetileno.

RMN: en DMSO

ppm 10,1 y 9	individual	2 H	Triazol carga +
" 8,4 y 7,1	individual	2 H	Triazol carga +
" 7,3-6,8	sist.complejo	3 H	Aromáticos
" 7,05	individual	2 H	grupo amínico
" 6,7	individual	1 H	Hidróxido
" 4,9-4,6	cuart-indiv.	4 H	Metileno

Ejemplo 3

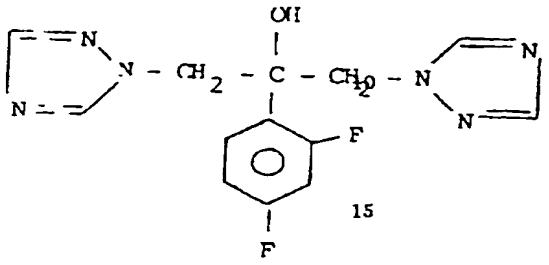
2-(2,4-difluorofenil),1,3-bis-(1H-1,2,4-triazol-1-il) 2 -propanol (I).

Se disuelven 6,3 del producto obtenido en el ejemplo 2 en 60 ml de agua y, enfriando a 5°C, se añade 1,8 g de ácido clorhídrico concentrado. Se trata la solución, a una temperatura entre 0 y 5°C, con una solución de 1,2 g de sodio-nitrito en 6 ml de agua. Se prosigue la reacción a la misma temperatura durante 30 minutos y después durante 1 hora más 20°C. La solución así obtenida se adiciona con 500 mg de carbón activo y se filtra. La solución limpia así obtenida es tratada con amoníaco concentrado hasta un pH 9, manteniéndole a 20°C. Cuando se inicia la precipitación del producto se enfría a 5°C por cuando menos 2 horas. Se filtra el precipitado que se lava en el filtro con 5 ml de agua. El bruto obtenido se cristaliza con 25 ml de alcohol isopropílico. Se lava el producto filtrado con 5 ml de alcohol isopropílico frío, desecado al vacío a 40°C.

Se obtienen 4,1 g (85,4 d.t.) de producto citado, idéntico por análisis centesimal, masa, espectro IR y RMN a una muestra de producto obtenido según la patente británica 2.099.818.

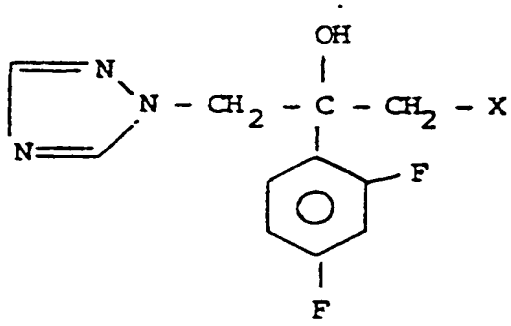
REIVINDICACIONES

1. Procedimiento para la preparación del compuesto de fórmula I



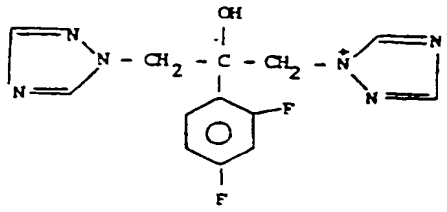
(I)

caracterizado porque comprende reaccionar un compuesto de fórmula II



(II)

donde X es fluoro, cloro, bromo o yodo, con 4-amino-1,2,4 -triazol para dar el compuesto de fórmula III



(III)

que se hace reaccionar con ácido nitroso.

2. Procedimiento según la reivindicación 1, caracterizado por el hecho de que se emplea un compuesto II en el que X es bromo.

Characterization of Polymorphic Forms of Fluconazole Using Fourier Transform Raman Spectroscopy

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Received March 13, 1995, from the *Ontario Laser and Lightwave Research Centre, Resource Facility, 60 St. George Street, Suite 331, Toronto, Ontario, Canada M5S 1A7, and †Nu-Pharm Inc., 380 Elgin Mills Road East, Richmond Hill, Ontario, Canada L4C 5H2.* Accepted for publication September 5, 1995[⊗].

Abstract □ Detailed Fourier transform Raman spectra of fluconazole have been recorded and the main spectral features of fluconazole have been assigned to its vibrational modes. Two different polymorphic forms of fluconazole were identified in two spectral regions, 150–1700 cm^{-1} and 2700–3200 cm^{-1}, respectively. The FT-Raman results agree well with those of differential scanning calorimetry and X-ray powder diffractometry. The combination of definiteness with easy sample handling makes FT-Raman spectroscopy a valuable technique for the analysis of polymorphs.

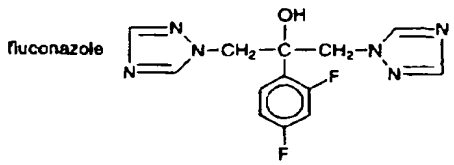
Characterization of polymorphic forms constitutes an important aspect of drug development. Different polymorphs of a drug may exhibit significantly different biological activities due to their different solubility and dissolution rate.[1] The stability and acceptability of the formulation may also be affected by different polymorphs. There are several techniques for analyzing polymorphs, including differential scanning calorimetry (DSC), optical microscopy, infrared spectroscopy, solid state NMR[2], and X-ray powder diffraction, which is the most widespread method. Recently, Fourier transform (FT) Raman spectroscopy has emerged as a new technique for differentiation and quantitative analysis of polymorphs.[3,4] The main advantage of FT-Raman is that no sample preparation is required, and the polymorphic form of the sample will not be changed. The Raman spectrum is obtained by collecting back-scattered light from either a powder or a formulation. It is well-known that some polymorphic forms may interconvert under high pressure, by the grinding involved in sample preparation or by the heating process used in DSC measurement.[5] Therefore, the FT-Raman technique is more suitable for studying certain polymorphs.

There are other advantages of FT-Raman spectroscopy over IR spectroscopy. Vibration modes involving symmetric and nonpolar bonds, which are normally IR inactive, give strong intensities in Raman spectra. The interference from water, usually strong in IR, is minimal in Raman spectra. The spectral region between 40 and 400 cm^{-1}, normally not available with an IR spectrometer, can easily be measured with an FT-Raman spectrometer. In fact, most lattice vibrational modes in crystals fall in this region.

In this paper, FT-Raman spectra of two polymorphs of fluconazole are presented. The different polymorphs were identified and characterized using FT-Raman spectroscopy, differential scanning calorimetry, and X-ray powder diffractometry.

Experimental Section

The Raman spectra were measured using a MB157 based FT-Raman/FT-IR spectrometer (Bomem, Hartmann & Braun Inc.). The excitation source was a Nd:YAG laser (Antares 76-s, Coherent Inc.) operating at 1.064 μm with a power stability of better than 1% root mean square. An InGaAs detector used in the spectrometer covers a Raman shift range from 150 to 3700 cm^{-1}. The laser beam is focused down to a 0.5-mm spot at the sample which is placed at the focus of an ellipsoidal mirror. The scattered light is collected by this mirror and directed into the MB157 near-IR spectrometer. A laser power of about 100 mW at the sample was used. The samples (a few milligrams of powder) were placed in a glass capillary tube and their spectra were collected with an instrumental resolution of 4 cm^{-1} for 200 scans.



Powder X-ray diffraction patterns of two fluconazole samples were obtained using a Siemens D-5000 diffractometer with a Cu Kα radiation source and a solid-state Peltier-cooled detector (Kevex 4608) as a secondary monochrometer. The samples were run over the most informative range from 5° to 35°/2θ. The step scan mode was performed with a step size of 0.02° at a rate of 1.2 step/s. The thermograms were measured using a differential scanning calorimeter (Mittler TC11 with a TA4000 processor) at a heating rate of 0.5 °C/min from 130 to 145 °C. A ca. 3–5 mg sample was sealed in an aluminum pan with a pierced hole under normal (air) atmosphere.

Fluconazole, 2-(2,4-difluorophenyl)-1,3-bis(1*H*-1,2,4-triazol-1-yl)-propan-2-ol, classified as an antifungal agent, has high oral efficacy with water solubility.[6] Samples A and B were obtained from two different manufacturers, as suppliers A and B, respectively.

Results and Discussions

FT-Raman spectra of two fluconazole samples over the frequency range of 150–1700 cm^{-1} and 2700–3250 cm^{-1} are compared in Figure 1. Both spectra appear complex with more than 60 well-resolved peaks in the fingerprint region of 500–1700 cm^{-1}. Such complex spectra are not unexpected since fluconazole contains several functional groups such as triazolyl, 2,4-difluorobenzyl, and hydroxy in addition to a propyl backbone. These functional groups exhibit some characteristic bands and an assignment of the bands (see Table 1) was made by comparing the wavenumbers and intensities of these bands with the Raman spectra of 1,2,4-triazole (98%, Aldrich Chemical Co.) and 2,4-difluorobenzyl alcohol (99%, Aldrich Chemical Co.), respectively (spectra are not shown). The different Raman spectra of fluconazole for samples A and B indicated that they belong to two different polymorphic forms. This assessment was confirmed by the DSC thermograms and by the X-ray diffraction patterns. The possibilities of pseudopolymorphs due to solvate or hydrate were excluded based on the thermogravimetric analysis of both samples.

The strongest Raman band of fluconazole is the ring breathing mode of the 2,4-difluorobenzyl group at 734 and 737 cm^{-1} for samples A and B, respectively. Since the ring structure is relatively rigid, only a small shift was observed for two different polymorphs. The ring breathing mode of 2,4-

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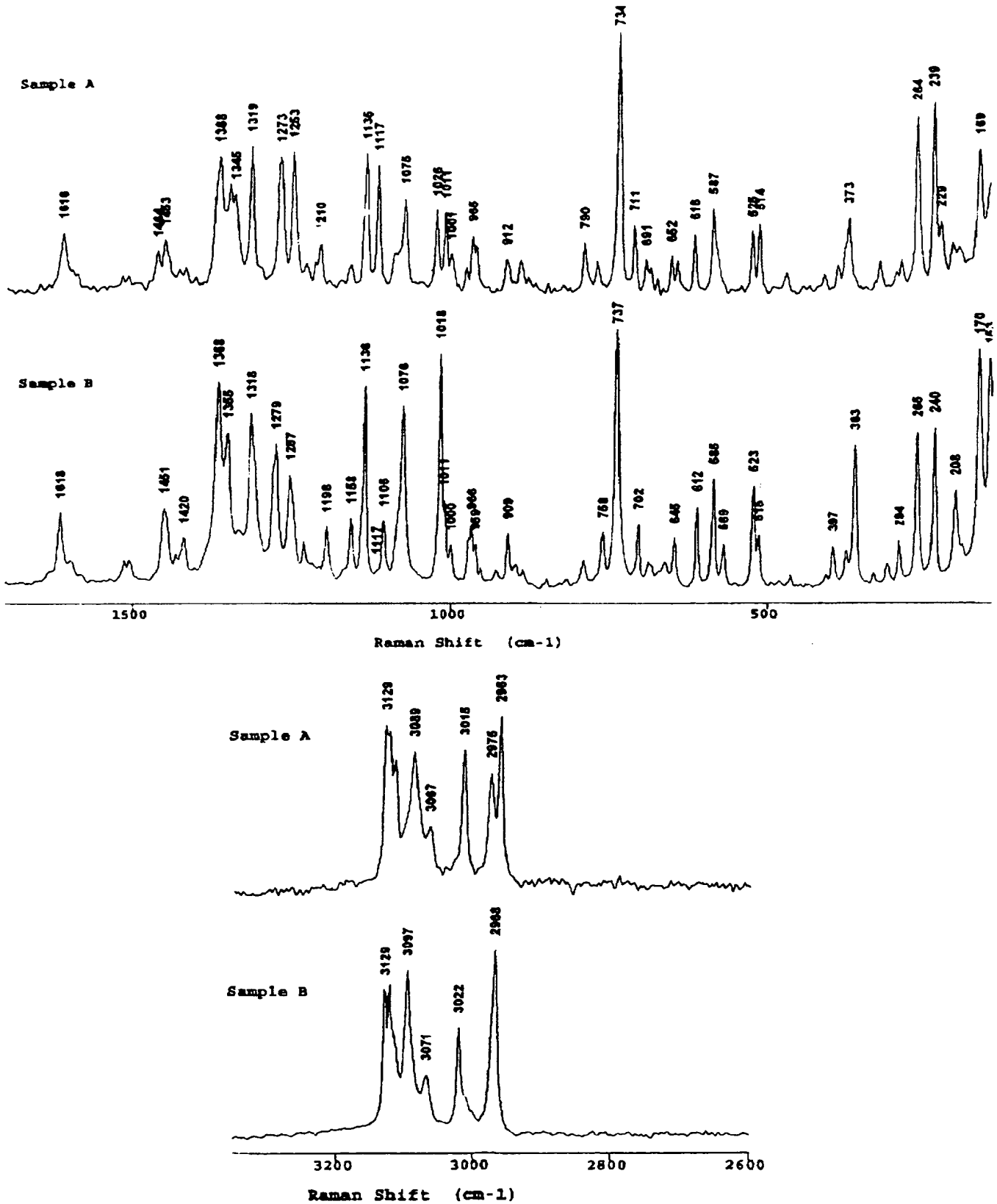

Figure 1—FT-Raman spectra of fluconazole samples A and B.

Table 1—Main Vibrational Modes Observed in the FT-Raman Spectra of Fluconazole Samples

Wavenumber (cm^{-1})		
Sample A	Sample B	Assignment
	Triazole Group[9]	
3129s	3129s	CH stretch
1368s	1368s	ring stretch
1253s	1257s	ring stretch
1135s	1136s	ring breath
965m	966m	ring bend
	2,4-Difluorobenzyl Group	
3089s	3097s	CH stretch
3015s	3022s	CH stretch
1616m	1618m	C=C stretch
1273s	1279s	CF stretch
1075s	1076s	CH deform
734 vs	737vs	ring breath
587m	585m	ring deform
	Propane Backbone	
2975s	2968s	CH_2 stretch
2963s		
1464m	1451m	CH_2 scissor
1453m		
1353m	1355m	CH bend
1117s	1106m	C–C stretch
1026m	1018s	C–(OH) stretch

difluorobenzyl alcohol at 733 cm^{-1} is also the strongest band in its spectrum. Another characteristic band in Figure 1 is the ring breathing mode of the triazole group at 1135 and 1136 cm^{-1} for sample A and B, respectively. The ring breathing mode of triazole was observed at 1146 cm^{-1}.

There are two spectral regions which show clear differences in the Raman spectra of sample A and B. The first region of interest is 1000–1150 cm^{-1}. The band at 1026 cm^{-1} in the spectrum of sample A is shifted to 1018 cm^{-1} in the spectrum of sample B with an enhanced intensity. This band was assigned to the C–(OH) stretching vibration. This shift was expected considering that polymorphs often exhibit different hydrogen-bonding networks.[7] Another band at 1117 cm^{-1} in the spectrum of sample A is shifted to 1106 cm^{-1} with a reduced intensity in the spectrum of sample B. This band was assigned to the C–C stretching mode in the propyl backbone. These two bands show larger shifts in the spectra of the two polymorphic forms as compared to the shifts of the breathing modes of the triazole and difluorobenzyl ring groups. This is due to the fact that when molecules are packed together in different arrangements in crystals (i.e. polymorphism) the vibrational mode involving less rigid bonds will be affected more than those of rigid structures. The second region of interest is the C–H stretching bands between 2950–3140 cm^{-1}. The C–H stretching modes tend to be weak in the IR due to low polarity, however, they are relatively strong in the Raman spectrum. The bands at 3089 and 3015 cm^{-1} in the spectrum of sample A, assigned to the C–H stretches of the difluorobenzyl group, are shifted to 3097 and 3022 cm^{-1}, respectively, in the spectrum of sample B. The C–H stretch band of CH_2 in the propyl backbone at 2968 cm^{-1} in the spectrum of sample B is split into two bands at 2963 and 2975 cm^{-1} in the spectrum of sample A.

Other features which show the differences in the Raman spectra of the two polymorphic samples are the band splittings. Bands at 1451 and 2968 cm^{-1} in the spectrum of sample B are split into doublets of ~12 cm^{-1} apart in the spectrum of sample A. This kind of band splitting can occur when the symm try of the molecule is violated, leading to the decoupling of normally degenerative vibrational modes. These

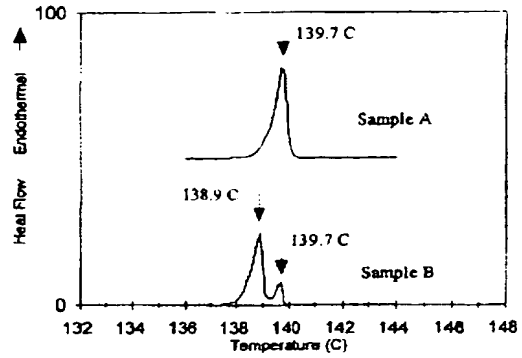

Figure 2—DSC thermograms of fluconazole samples A and B.

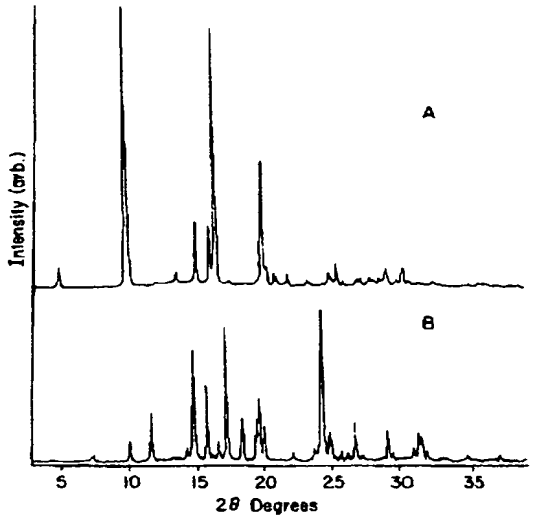

Figure 3—X-ray diffraction patterns of fluconazole samples A and B.

band splittings occur to the vibrational modes of CH_2 in the propane backbone, which is less rigid than the triazole and difluorophenyl rings. The low-frequency modes, arising largely due to lattice vibrations, are very sensitive to structural changes in the solid state. For example, the band at 229 cm^{-1} in the spectrum of sample A cannot be found in the spectrum of sample B. The intensity of the 208 cm^{-1} band in the spectrum of sample B is substantially reduced in the spectrum of sample A. The spectral differences in this region between two polymorphs can be explained by the differences in intermolecular interactions and differences in crystal symmetry in the two forms.

The DSC thermograms of the two fluconazole samples are shown in Figure 2. One endothermic peak at 139.7 °C was found for sample A, indicating a single polymorphic form (I). The other sample exhibits a main endothermic peak at 138.9 °C and a smaller peak at 139.7 °C, indicating that it consists mainly of another polymorphic form (II) and possibly a small amount of the form I. However, it is also possible that a small amount of form II transformed into form I during the heating process.

The X-ray diffraction patterns of samples A and B of fluconazole are shown in Figure 3. The main diffraction peaks of sample A are observed at 2θ = 10.0°, 15.0°, 16.0°, 16.6°, and 20.0°, and those of sample B are observed at 2θ = 11.6°, 14.7°, 15.8°, 17.3°, 18.4°, 19.5°, and 24.4°. The X-ray results show that the sample A consists of only one polymorphic form (I), however, the sample B consists of mainly (90%) of another

polymorphic form (II) and a small amount (10%) of polymorphic form I since the strong peaks at 10.0°, 16.6°, and 20.0° in pattern A also appear in pattern B although with much reduced intensities. The 10% polymorphic form I in sample B was calculated from the ratio of integrated intensities of the peak at 10.0° in both patterns.

The Raman bands in Figure 1 have an average bandwidth at half of their intensity of ~8 cm^{-1}. At 10% of their intensity, the bandwidth is broadened to ~20 cm^{-1}. Since most of the band shifts and splittings due to polymorphism are about 10 cm^{-1} or less, the 10% polymorph I in sample B would contribute only to the shoulders and tails of the Raman bands of polymorph II and consequently would be difficult to quantify. The band at 1117 cm^{-1} in the spectrum of polymorph I (A) is an exception. Because of its large shift (11 cm^{-1}) in the spectrum of polymorph II, it can still be observed in the spectrum of sample B. The quantitative analysis of binary polymorphic mixtures by FT-Raman spectroscopy was reported recently.[8] However, it requires pure polymorphic samples which are not available for fluconazole polymorphs.

Conclusions

From the data presented in this paper, it is evident that two polymorphs, I and II, of fluconazole can be readily differentiated using FT-Raman spectroscopy. The differences of the two polymorphs are characterized by the band shiftings and splittings in their Raman spectra. The existence of two polymorphs in fluconazole is also confirmed by the DSC thermograms and by the X-ray powder diffraction patterns. The fact, however, that the two polymorphs can be readily characterized without the need for sample preparation shows the great potential of FT-Raman spectroscopy in pharmaceutical analysis.

References and Notes

1. Haleblian, J. K.; Koda, R. T.; Biles, J. A. *J. Pharm. Sci.* **1971**, *60* (10), 1488–1491.
2. Lin, S.-Y. *J. Pharm. Sci.* **1992**, *81* (6), 572–575.
3. Deeley, C. M.; Spragg, R. A.; Threlfall, T. L. *Spectrochimica Acta.* **1991**, *47A* (9/10), 1217–1223.
4. Neville, G. A.; Beckstead, H. D.; Shurvell, H. F. *J. Pharm. Sci.* **1992**, *81* (12), 1141–1146.
5. Chan, H. K.; Doelker, E. *Drug Dev. Ind. Pharm.* **1985**, *11*, 315.
6. Richardson, K.; Brammer, K. W.; Marriott, M. S.; Troke, P. F. *Antimicrob. Agents Chemother.* **1985**, *27* (5), 832–835.
7. Paul, S. O.; Schutte, C. J. H.; Hendra, P. J. *Spectrochimica Acta* **1990**, *46A* (2), 323–329.
8. Tudor, A. M.; Church, S. J.; Hendra, P. J.; Davies, M. C.; Melia; C. D. *Pharm. Res.* **1993**, *10*, 1772–1774.
9. The vibrational spectra and normal coordinate calculations of 1,2,4-triazole were reported: Bougeard, D.; Le Calve, N.; Saint Roch, B.; Novak, A. *J. Chem. Phys. 64*, (12), **1976**, 5152–5164.

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